Chapter 9

Adrenergic Drugs
Objectives

- To understand the pharmacological effects
- The mechanisms of drug action
- Therapeutic applications of alpha and beta adrenergic agonists
### Adrenoceptor and subtypes

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonist</th>
<th>Antagonist</th>
<th>Effects</th>
<th>Gene on Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$ type</td>
<td>Phenylephrine</td>
<td>Prazosin</td>
<td>$\uparrow$ IP3, DAG common to all</td>
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</tr>
<tr>
<td>$\alpha_{1A}$</td>
<td></td>
<td></td>
<td></td>
<td>C5</td>
</tr>
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<td>$\alpha_{1B}$</td>
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<td>C8</td>
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<td>C20</td>
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<tr>
<td>$\alpha_2$ type</td>
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<td>Yohimbine</td>
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<td>Oxymetazoline</td>
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<td>Prazosin</td>
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<td>$\alpha_{2C}$</td>
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<tr>
<td>$\beta$ type</td>
<td>Isoproterenol</td>
<td>Propranolol</td>
<td>$\uparrow$ cAMP common to all</td>
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<td>$\beta_1$</td>
<td>Dobutamine</td>
<td>Betaxolol</td>
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<td>$\beta_2$</td>
<td>Albuterol</td>
<td>Butoxamine</td>
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<td>$\beta_3$</td>
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<tr>
<td>Dopamine type</td>
<td>Dopamine</td>
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<td>$\uparrow$ cAMP</td>
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<td>Fenoldopam</td>
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<tr>
<td>$D_2$</td>
<td>Bromocriptine</td>
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<td>$\downarrow$ cAMP</td>
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<td>$\downarrow$ cAMP</td>
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<td>$D_4$</td>
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<td>$D_5$</td>
<td></td>
<td></td>
<td>$\uparrow$ cAMP</td>
<td>C4</td>
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</tbody>
</table>
Biological functions

- smell and taste
- (~1000 types of receptors)
- perception of light
- neurotransmission
- function of endocrine and exocrine glands
- chemotaxis
- exocytosis
- control of blood pressure
- embryogenesis
- development
- cell growth and differentiation
- HIV infection
- oncogenesis

G-protein coupled receptors:

- $\alpha_i$ (ion channels, inhibition of cAMP, phospholipases, phosphodiesterases)
- $\alpha_s$ (increase cAMP)
- $\alpha_q$ (GTP)
- $\alpha_{12}$ (GTP)

PIP2 $\rightarrow$ DAG $\rightarrow$ IP3
Receptor regulation

Heterologous Desensitization

Loss response for the receptor that has not been directly activated

Betta adrenoceptor

AC

cAMP

PKA, PKC

Second messengers
Homologous desensitization: loss response because of receptor exposed to repeated or sustained stimulation.

Signaling pathway of $\alpha_1$ receptor activation
Signaling pathway of $\beta$ and $\alpha_2$ receptor

NORADRENALINE
DOBUTAMINE
ISOPROTERENOL

a2 receptor

NORADRENALINE
CLONIDINE
<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Most vascular smooth muscle (innervated)</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contraction (dilates pupil)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Erects hair</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Increases force of contraction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Postsynaptic CNS adrenoceptors</td>
<td>Probably multiple</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation</td>
</tr>
<tr>
<td></td>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibition of transmitter release</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Fat cells</td>
<td>Inhibition of lipolysis</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Heart</td>
<td>Increases force and rate of contraction</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Respiratory, uterine, and vascular smooth muscle</td>
<td>Promotes smooth muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td>Promotes potassium uptake</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>Activates glycogenolysis</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>Fat cells</td>
<td>Activates lipolysis</td>
</tr>
<tr>
<td>$D_1$</td>
<td>Smooth muscle</td>
<td>Dilates renal blood vessels</td>
</tr>
<tr>
<td>$D_2$</td>
<td>Nerve endings</td>
<td>Modulates transmitter release</td>
</tr>
</tbody>
</table>
Effects of stimulation of $\alpha_1$ adrenergic receptors

(1) $\alpha_1 R \xrightarrow{Gq} PLC \rightarrow Ca^{2+}$

- Constriction of vascular smooth muscle
- Dilation of pupil
- Cardiac contraction $\uparrow$
- Contraction of gastrointestinal and genitourinary sphincter
Effects of stimulation of $\alpha_2$ adrenergic receptors

$\text{Go} \rightarrow \text{Ca}^{2+} \downarrow$

(2) $\alpha_2R \xrightarrow{\text{Gi}} \text{adenylyl cyclase} \downarrow \rightarrow \text{K}^+ \uparrow$

Effects

- inhibition of transmitter release
- induction of platelet aggregation
- relaxation of gastrointestinal smooth muscle
- peripheral vasodilation
Effects of stimulation of $\beta$–adrenergic receptors

Gs $\rightarrow$ Ca$^2^+$

(3) $\beta_1$R $\rightarrow$ Gs $\rightarrow$ adenylyl cyclase $\rightarrow$ cAMP $\rightarrow$ PKA

Effects

- Force of contraction, rate of heart
- Rennin secretion
- NA release
Effects of stimulation of $\beta$-adrenergic receptors

(4) $\beta_2R \xrightarrow{Gs} \text{adenylyl cyclase} \xrightarrow{\uparrow} \text{cAMP} \xrightarrow{\uparrow} \text{PKA}$

Effects

- Relaxation of vascular, bronchial, gastrointestinal, genitourinary smooth muscle
- Promotion of glycogenolysis of skeletal muscle

(5) $\beta_3R$ promotion of glycogenolysis of liver
Pharmacological responses of $\alpha$ and $\beta$–R agonists

1. Cardiovascular system---

**Heart:** $\beta_1$

a. Heart rate $\uparrow$

b. Cardiac output

c. Cardiac contraction $\uparrow$

d. Cardiac conduction $\uparrow$
Vascular effects

a. $\alpha_1 R$---resistance $\uparrow$
   (vascular contraction)

b. $\beta_2 R$---resistance $\downarrow$
   \hspace{1cm} vascular relaxation
   (coronary artery, skeletal muscle vessels)
<table>
<thead>
<tr>
<th></th>
<th>Phenylephrine</th>
<th>Epinephrine</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular resistance (tone)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous, mucous membranes (α)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>0</td>
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<tr>
<td>Skeletal muscle (β₂, α)</td>
<td>↑</td>
<td>↓ or ↑</td>
<td>↓</td>
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<tr>
<td>Renal (α, D₁)</td>
<td>↑↑</td>
<td>↓ or ↑²</td>
<td>↓</td>
</tr>
<tr>
<td>Splanchnic (α, β)</td>
<td>↑↑↑</td>
<td>↓ or ↑²</td>
<td>↓</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>↑↑↑</td>
<td>↓ or ↑²</td>
<td>↓</td>
</tr>
<tr>
<td>Venous tone (α, β)</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Contractility (β₁)</td>
<td>0 or ↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Heart rate (predominantly β₁)</td>
<td>↓↓ (vagal reflex)</td>
<td>↑ or ↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0, ↓, ↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td><strong>Blood pressure</strong></td>
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<tr>
<td>Mean</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Diastolic</td>
<td>↑↑</td>
<td>↓ or ↑²</td>
<td>↓</td>
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<tr>
<td>Systolic</td>
<td>↑↑</td>
<td>↑</td>
<td>0 or ↓</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0</td>
<td>↑↑</td>
<td>↑</td>
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</tbody>
</table>

¹↑↑ = increase; ↓ = decrease; 0 = no change.
²Small doses decrease, large doses increase.
Sympathomimetics are drugs that partially or completely mimic the action of EPINEPHRINE (E) or NOREPINEPHRINE (NE)
   - DIRECTLY – acts on adrenergic receptor
   - INDIRECTLY – stimulates the release CATECHOLAMINES (CA) from nerve ending

Classifications: the endogenous biogenic amines (NE, E, DA, ISO)
   ephedrine and other vasocontractors
   bronchodilators
   CNS stimulants

Their effects can be predicted from the knowledge of:
1. The type of adrenergic receptor
2. Property for penetration into CNS
3. Receptor selectivity
2. **Eye**
   
   MYDRIASIS (radial pupillary dilator muscle of iris contains $\alpha$ receptors, $\alpha$ stimulation $\rightarrow$ muscle contraction $\rightarrow$ pupil dilation)

3. **Respiratory tract**
   
   Bronchial smooth muscle: $\beta_2$ receptor $\rightarrow$ relaxation $\rightarrow$ bronchodilation
   
   Upper respiratory tract mucosa: $\alpha$ receptors; $\alpha$ stimulants $\rightarrow$ decongestion

4. **Gastrointestinal tract**
   
   Both $\alpha$ and $\beta$ stimulants induce the relaxation of GIT smooth muscle

   $\beta$ receptor activation (smooth muscle cells) $\rightarrow$ hyperpolarization $\rightarrow$ relaxation
   
   $\alpha$ stimulants act indirectly; reduce presynaptically the release of acetylcholine
5. Genitourinary tract

Human uterus (α and β receptors). β2 receptor stimulation → relaxation
Bladder base and urethral sphincter: α receptor → contraction → continence
Bladder wall: β2 receptors → relaxation
Ejaculation is dependent upon normal α receptor activity

6. Exocrine glands

Salivary gland: increased secretion (mucinous rich saliva,)
Apocrine sweat gland (eg. palms of hands): α stimulants → sweat production↑
7. **Metabolic effects**

*Fat cells*: $\beta_3$ receptor activation $\rightarrow$ increased lipolysis

*Lipocytes*: $\alpha_1$ receptor activation $\rightarrow$ inhibited lipolysis

*Liver*: $\beta_2$ & $\alpha_1$ receptor activation $\rightarrow$ glycogenolysis $\rightarrow$ blood glucose $\uparrow$

*Skeletal muscle*: $\beta_1$ receptor activation $\rightarrow$ glycogenolysis $\rightarrow$ lactate $\uparrow$

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8. **Endocrine function**

*Insulin secretion* is stimulated by $\beta_1$ and inhibited by $\alpha_2$ stimulation

*Renin secretion* is stimulated by $\beta_1$ and inhibited by $\alpha_2$ receptors
9. Other effects

Skeletal muscle: $\beta_2$ receptor stimulation $\rightarrow$ increased twitch tension in fast contracting muscles (white muscle) and reduced twitch in slow (red) muscles;

CNS: $\beta_2$ receptor agonists cause tremor, shakiness, accompanied by fear and excitement

Mast cells: histamine release is inhibited by $\beta_2$ receptors
### Classification:

<table>
<thead>
<tr>
<th>Relative Receptor Affinities</th>
<th>Alpha agonists</th>
<th>Mixed alpha and beta agonists</th>
<th>Beta agonists</th>
<th>Dopamine agonists</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Phenylephrine, methoxamine</td>
<td>α₁ &gt; α₂ &gt;&gt;&gt;&gt;&gt; β</td>
<td>Norepinephrine</td>
<td>Dobutamine¹</td>
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<td>Clonidine, methylnorepinephrine</td>
<td>α₂ &gt; α₁ &gt;&gt;&gt;&gt;&gt; β</td>
<td>Epinephrine</td>
<td>Isoproterenol</td>
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<td>Terbutaline, metaproterenol, albuterol, ritodrine</td>
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<td></td>
<td></td>
<td>D₁ = D₂ &gt;&gt; β &gt;&gt; α</td>
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<td></td>
<td>Fenoldopam</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D₁ &gt;&gt; D₂</td>
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</table>

¹See text.
### Chemistry and pharmacokinetics

Catechol (ortho-dihydroxybenzene) + an amino group on the side chain

**β-phenolamine**

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
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<tr>
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<td>OH</td>
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<td>CH3</td>
<td>CH3</td>
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</table>

**D**irect

**M**ixed

**I**ndirect
Endogenous catecholamines: - norepinephrine, epinephrine, dopamine
Synthetic catecholamines: - isoproterenol

**Substitutions:**

a.) *On the amino group*
   - Increasing the size of the alkyl group $\rightarrow$ increased $\beta$ and decreased $\alpha$ activity

b.) *On the benzene ring*
   - Maximal $\alpha$ and $\beta$ activity is found with CAs ($R_1$ and $R_2 = OH$)
   - Absence of one or two -OH increases bioavailability
   - Absence of -OH groups increases lipid solubility (potential CNS effects)

c.) *On the $\alpha$ carbon*
   - Substitution blocks the oxydation by MAO and prolongs the action
1. Cardiovascular applications
   a.) HYPOTENSION
   Sympathomimetics may be used in hypotensive emergency to preserve cerebral and coronary blood flow
   DRUGS: Direct acting $\alpha$ agonists: NE, Phenylephrine, Methoxamine

   b.) SHOCK
   THERAPY: volume replacement and treatment of underlying disease (vasoconstrictor or vasodilator therapy)

   c.) CARDIOGENIC SHOCK - usually due to massive myocardial infarction
   THERAPY: fluid replacement, optimize tissue blood flow rather than blood pressure.
d.) PAROXYSMAL TACHYCARDIA - Phenylephrine, Methoxamine

e.) HEART BLOCK - Isoproterenol, Epinephrine (in cardiac arrest),

f.) CONGESTIVE HEART FAILURE - Dobutamine, Dopexamine, Prenarterol

2. Conditions in which blood flow is reduced

- $\alpha$ receptor stimulation is desired:
  - In surgery for achieving hemostasis: Epinephrine,
  - Reducing mucous membrane congestion: Phenylephrine, ine,
  - (eg. hayfever, common cold): Xylametazoline
3. Respiratory applications
   Bronchial asthma - selective β2 agonists

4. Anaphylaxis - anaphylactic shock and related hypersensitivity reactions affect both respiratory and cardiovascular systems.
   SYMPTOMS: bronchospasm, mucous membrane congestion, angioedema, collapse
   THERAPY: Rapid subcutaneous injection of Epinephrine, Glucocorticoids, Antihistamines

5. Ophtalmic applications
   Phenylephrine - mydriatic, decongestant
   Epinephrine - glaucoma (intraocular pressure and humor formation ↓, humor outflow ↑)

6. Genito-urinary applications - β2 selective agonists relax pregnant uterus
   DRUGS: Ritodrine, Terbutaline

7. CNS applications - Amphetamine-like drugs → euphoric effect
   USE: narcolepsy, hyperkinetic syndrome in children
Adverse reactions

Anxiety, headache, cardiac arrhythmia, hypertension, cerebral hemorrhage.
SPECIFIC SYMPATHOMIMETIC DRUGS

A: CATECHOLAMINES

EPINEPHRINE (E, ADRENALINE)

Acts on both \( \alpha \) and \( \beta \) receptors (low concentration - \( \beta \) effects, high dose- \( \alpha \) effect dominated)

\( a) \) Effects on blood pressure

Low doses of E: \( \text{BP} \downarrow \) (\( \beta_2 \) receptor stimulation \( \rightarrow \) vasodilatation)

Large doses of E: \( \text{BP} \uparrow \) (\( \alpha \) receptor stimulation \( \rightarrow \) vasoconstriction)
b.) Vascular effects
(1) Decreased cutaneous blood flow (BF) (α)
(2) Increased BF to skeletal muscle (β2 - at low doses)
   Decreased BF to skeletal muscles (α - at high doses)
(3) Increased hepatic BF, decreased splanchnic vascular resistance (β2)
(4) Increased renal vascular resistance → decreased renal BF
(5) Increased arterial and venous pulmonary pressure
(6) Increased coronary flow
c.) **Effects on the heart**
   (1) Direct effect on the β1 receptors → contractility↑, HR ↑ (or ↓)
   (2) Increased stroke volume (SV) and cardiac output (CO)
   (3) Increased arrhythmogenesis

d.) **Effect on smooth muscles**
   This depends on the predominant type of the receptor in the muscle
   (1) GIT smooth muscle relaxation (α & β), sphincter contraction (α)
   (2) Uterine contractions: inhibited (β2) or stimulated (α) depending on the
       menstrual phase or the state of gestation
   (3) Bladder: detrusor relaxes (β2), trigone and sphincter contracts (α)
   (4) Bronchial smooth muscle: relaxes (β2)

e.) **Metabolic effects**
   (1) Increase in glucose and lactate production
   (2) Inhibition of insulin secretion (α)
   (3) Increase in FFA (β3)
   (4) Increase in oxygen consumption
NOREPINEPHRINE (NE, NORADRENALINE)

NE is almost equipotent with E on β1 and α receptors but with little effect on β2 receptors

**Pharmacokinetics of Epinephrine and Norepinephrine**

1. Poor absorption following oral administration (rapid conjugation and oxydation)
2. Slow absorption following subcutaneous administration → local vasoconstriction
3. Inhaled solutions are used in the disease of respiratory tract
4. They can be given intravenously
5. Metabolism in the liver (COMT and MAO); excretion in the urine
**Therapeutic uses of Epinephrine and Norepinephrine**

**EPINEPHRINE**
1. To treat bronchospasm
2. For relief hypersensitivity reactions (anaphylactic shock)
3. To prolong the effect of local anaesthetics (infiltrative)
4. To restore cardiac activity in cardiac arrest
5. In glaucoma (facilitates aqueous drainage)

**NOREPINEPHRINE** for treating hypotension (when tissue perfusion is good)
Preparations

Norepinephrine (Levophed) bitartarate, injection 1 mg/ml for iv. Infusion

Ethynorepinephrine hydrochloride (Bronkephrine), 2 mg/ml for sc. or im. inj. to relieve bronchospasm

Epinephrine hydrochloride, inj. from 0.01 to 1 mg/ml, for nasal administration, 0.1 and 2 % solutions used in ophtalmology

Epinephrine bitartarate aerosols (Medihaler-Epi, Primatene Mist Suspension, etc)

Epinephrine borate (Epinal, Eppy/N) 0.5 and 2 % ophtalmologic solutions

Dipivefrin hydrochloride (Propine) 0.1 % solution for the management of glaucoma
ISOPROTERENOL (ISO, ISOPRENALINE)

Potent $\beta$ receptor agonist

(1) Stimulates $\beta_1$ receptors in the heart $\rightarrow$ chronotropic and inotropic effect

(2) Stimulates $\beta_2$ receptors in vascular smooth muscle $\rightarrow$ vasodilatation
   $\quad$ in bronchial smooth muscle $\rightarrow$ bronchodilation
   $\quad$ in the uterus $\rightarrow$ uterus relaxation

(3) Stimulates $\beta_3$ receptors in fat cells $\rightarrow$ lipolysis

(4) Stimulates insulin secretion
Pharmacokinetics of ISO
(1) ISO does not absorb orally
(2) It is easily absorbed when given parenterally or inhaled aerosol
(3) It is principally metabolised by COMT

Therapeutic use of ISO
Cardiac stimulant and bronchodilator

Adverse effects of ISO
(1) These are similar to the undesired effects of E
(2) Overdosage can induce fatal VF
(3) Tolerance occurs with overuse as an antiasthmatic drug
B: NON-CATECHOLAMINES

PHENYLEPHRINE

Pure $\alpha$ receptor agonist, with long duration of action (not inactivated by COMT)
(1) Direct acting sympathomimetic, its effects are similar to those of NE but less potent
(2) Vasoconstriction, BP $\uparrow$, reflex bradycardia occurs after parenteral administration

**Therapeutic uses**
(1) nasal decongestant
(2) pressor agent
(3) local vasoconstrictor - as 10 % ophtalmic solution
   - as an adjunct for use of LA
(d) for relief of paroxysmal atrial tachycardia

**Adverse effects**
(1) Large doses $\rightarrow$ ventricular arrhythmias (eg. after systemic absorption)
(2) Rebound nasal congestion may occur after chronic use
METHOXAMINE (Methoxamine hydrochloride, Vasoxyl)
(1) Its pharmacologic actions are similar to those of Phenylephrine
(2) Directly acts as $\alpha$ receptor agonist $\rightarrow$ prolonged increase in BP, vagally mediated bradycardia
(3) Weak CNS effects
(4) For hypotensive (20 mg/ml) and paroxysmal atrial tachycardia
EPHEDRINE

Pharmacologic actions

(1) Mixed agonist - it has both direct and indirect actions
(2) Following iv. administration its action is similar to that of E, but with weaker potency and long-lasting action on blood pressure
(3) CNS stimulation → insomnia, nervousness, nausea, agitation
(4) Tachyphylaxis could occur with repeated administration
**Pharmacokinetics**

(1) It is absorbed when taken orally
(2) It is resistant to COMT and MAO → prolonged action

**Therapeutic use**

(1) In the treatment of bronchial asthma
(2) As a nasal decongestant
(3) As a mydriatic

**Adverse effects**

(1) Similar to the undesired effects of E
(2) CNS effects may occur
(3) It must be used with caution in patients with cardiovascular diseases

**Preparations**

**Ephedrine sulphate** (Vatronal) 25 and 50 mg capsules, 0.5 % nose drops, 25 and 50 mg/kg injection for vasoconstriction
XYLOMETAZOLINE, OXYMETAZOLINE and NAPHASOLINE

(1) Direct $\alpha$ agonists, used as a nasal decongestants.
(2) Following continuous use they may induce chronic rhinitis (rebound swelling)
(3) Systemic effects: hypertension, dizziness, palpitation, CNS stimulation

Xylometazoline hydrochloride (Otrivin) 0.05 and 0.1 % nose drops
Oxymetazoline hydrochloride (Afrin) 0.025 and 0.05 % nose drops,
0.025 % eye drops
L-Desoxyephedrine (Vicks) for inhalation
C: RECEPTOR SELECTIVE SYMPATHOMIMETIC DRUGS

1. $\alpha_2$ receptor selective drugs: CLONIDINE, GUANFACINE, GUANABENZ
   Potent antihypertensive drugs

2. $\beta$ receptor selective drugs (separation of $\beta_1$ and $\beta_2$ effects)
   (1) $\beta_1$ receptor selective drugs: DOBUTAMINE, PRENARTEROL
      They increase cardiac output without changes in HR.
      Tolerance can develop.

Use: Congestive heart failure
(2) β2 receptor selective drugs: in asthma therapy and uterus relaxants

**Therapeutic uses:** Bronchial asthma, bronchospasm
Caution in patients with cardiovascular disease, hyperthyreodism

And β2 receptor stimulating uterus relaxants → to avoid premature labor

**Adverse effects:** tachycardia, tremor
Contraindications: cardiovascular disease, hyperthyreodism